[P11] Molecular dynamics-based elucidation of neutraligand binding to chemokine CXCL12

Tim Knehans[1], Esther Kellenberger[1], Didier Rognan[1]

[1]*Laboratoire d'Innovation Thérapeutique, Université de Strasbourg, France*

The C-X-C motif chemokine ligand 12(CXCL12) is the sole chemokine ligand for the chemokine receptor CXCR4. As such, it is an important factor in a series of developmental processes including hematopoiesis, cardiogenesis, vascular formation, neurogenesis and maintenance of tissue stem cells as well as being significant in various cancer cell functions such as migration, invasion, and survival [1-2]. The disruption of the interactions between CXCL12 and CXCR4 has been at the center of research to address CXCL12 and CXCR4 mediated diseases with the primary success being the development of antagonists of the chemokine receptor [3]. In 2008, a neutraligand featuring a chalcone scaffold (chalcone4) has been identified as an inhibitor of CXCR4 function while exclusively binding to the chemokine [4]. However, the exact structural nature of the complex remains elusive to this day.

Herein we will present the analyses and elucidation of interaction between chalcone4 and CXCL12 through the application of explicit solvent molecular dynamics simulations. Multi-microsecond simulation protocols for both monomeric and dimeric CXCL12 were conducted to model the association of unbound chalcone4 with the chemokine. Subsequent clustering-based analyses indicated that the preferred site of interaction of chalcone4 would directly displace a sulfonylated N-terminal tyrosine of CXCR4 which has been identified as being significant for the signaling process [5]. To confirm the successful modeling of the complex, a series of mutants which disrupt the putative binding modes has been proposed. Additionally, the results were incorporated into a drug development campaign aimed at the discovery of novel drug-like compounds binding to CXCL12.

Bibliography:

[1] L.T; K.O. Leukemia 16 (2002) 1992-2003
[2] B.F. Nat.Rev.Cancer. 7 (2004) 540-550
[3] D.B; X.S;G.F;G.A;N.N. Theranostics. 1 (2013**)** 47-75
[4] HH.M; B.K; R.F; P.F; F.C; L.S. J.Biol.Chem. 283 (2008) 23189-23199
[5] F.M;B.GJ;V.N;W.PL;K.E;M.T;C.H. J. Biol. Chem. 277 (2002) 29484-29489